EXHIBIT A68

Use of cosmetic talc on contraceptive diaphragms and risk of ovarian cancer: a meta-analysis of nine observational studies

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Prior work suggests an association between perineal use of cosmetic talc and increased ovarian cancer risk. A meta-analysis was performed to examine this hypothesis by evaluating ovarian cancer risk associated with direct exposure of the female genital tract to talc via dusting of contraceptive diaphragms. Data were pooled from epidemiological studies using a general variance-based meta-analytic method that employs confidence intervals. The outcome of interest was a summary relative risk reflecting the risk of ovarian cancer development associated with the use of cosmetic talc on contraceptive diaphragms. Sensitivity analyses were performed to explain any observed statistical heterogeneity and to explore the influence of specific study characteristics on the summary estimate of effect. Initially, combining homogeneous data from nine case–control studies yielded a non-statistically significant summary relative risk of 1.03 (0.80–1.37), suggesting no association between talc-dusted diaphragms and ovarian cancer development. Sensitivity analyses were performed to evaluate the robustness of this finding. All resultant summary relative risks were not statistically significant. The available epidemiological data do not support a causal association between the use of cosmetic talc-dusted diaphragms and ovarian cancer development. *European Journal of Cancer Prevention* 16:422–429 © 2007 Lippincott Williams & Wilkins.

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Introduction

Ovarian cancer represents a major cause of cancer-related morbidity and mortality in the United States with an estimated 22 000 new cases diagnosed in 2005 (Boger-Meigiddo and Weiss, 2005). It is the seventh most common cancer in women and ranks fourth as a cause of cancer deaths among female individuals from the United States, with some 16 000 succumbing to the disease this year. The lethality of ovarian tumors is in large part due to the fact that clinical symptoms tend to occur late in the natural history of the disease and the lack of screening tests allowing for early diagnosis. In fact, approximately 60% of patients are diagnosed with late-stage disease (stage III and IV) vastly diminishing the chance of long-term survival (approximately 10% at 5 years from diagnosis) (Richardson *et al.*, 1985).

Primary prevention of ovarian cancer remains elusive as a clear etiology for the vast majority of cases is unknown. Nonetheless, prior epidemiological research suggests a number of risk factors, including age (older versus younger), nulliparity, first pregnancy after the age of 35 years, diet high in saturated fats, positive family history of ovarian/breast cancer and race (white versus African American) (Baker and Piver, 1994; Tortolero-Luna and Mitchell, 1995; Daly and Obrams, 1998). Clear geographic differences in incidence exist. The highest rates are found in industrialized countries versus underdeveloped nations (Ioka *et al.*, 2003), implicating environmental factors in ovarian cancer etiology. The one exception is highly industrialized Japan (Ioka *et al.*, 2003) with a low annual incidence of approximately 3/100 000. Interestingly, Japanese woman who migrate to the United States experience an increased occurrence of this disease, further suggesting environmental factors in its cause.

In 1982, Cramer *et al.* (1982) published the first study suggesting a link between use of cosmetic talc and the risk of developing ovarian cancer. Subsequently, a number of additional reports have shown a small but increased risk among women using cosmetic talc products, although this finding is not universal (Chang and Risch, 1997). These statistical associations raise concerns that a cause–effect relationship may exist between talc exposure (particularly perineal use) and ovarian carcinogenesis.

Further fueling concerns about this association is the mistaken, but often repeated, assertion that asbestos and talc are biologically similar; that is, they may exhibit similar disease-causing potential (Wong *et al.*, 1999). While talc and asbestos are both silicates, they bear little resemblance structurally or in their biological properties. Asbestos fibers are well recognized human and animal carcinogens with substantial supporting epidemiological and in-vivo evidence available in the published literature (Huncharek, 1986; Mossman and Gee, 1989). Asbestos is known to induce peritoneal (and pleural) mesotheliomas among occupationally and environmentally exposed cohorts and some evidence exists suggesting that asbestos can also cause ovarian neoplasms in humans (Acheson *et al.*, 1982).

Although in the experimental setting translocation of talc particles to the human ovary can occur with deliberate or inadvertent manipulations of patients in the supine position (Wehner, 1998), it is unknown whether cosmetic use of talc in the perineal area can routinely penetrate the female reproductive tract and reach the ovary against physiological forces working in the opposite direction. The existing epidemiological literature focuses primarily on external perineal exposure. It appears, however, that the talc–ovarian cancer hypothesis could be tested with better precision and validity if the exposure to the suspected carcinogen was directly to the reproductive tract. A common route for such an exposure is via talc dusting of contraceptive diaphragms, a well documented practice in the relevant epidemiological literature. Intuitively, the possible association of ovarian cancer with talc-dusted diaphragms appears to provide a more rational test of this cause–effect hypothesis. Therefore, the present report describes the results of a meta-analysis pooling data from nine epidemiological studies examining the risk of ovarian cancer associated with the use of cosmetic talc on diaphragms.

Methods

The methods employed in the design and execution of this analysis have been previously described (Greenland, 1986; Cooper and Hedges, 1994). A study protocol was prospectively developed outlining the purpose and methods; that is, a meta-analysis examining the risk of developing ovarian cancer associated with use of talc-dusted contraceptive diaphragms. Eligibility criteria for study inclusion were determined prospectively as were the specific data elements to be extracted from each published report. The study protocol included details of the planned statistical analysis.

We used a data extraction form designed for recording relevant information from each selected report. Two researchers performed data extraction with differences in extraction forms resolved by consensus. Other data collected but not included in the eligibility criteria were the number of patients in each study, study odds ratios or relative risks, 95% confidence intervals and type of statistical adjustments made, if any, by individual study authors.

Literature search

Information retrieval was performed by previously described methods (Cooper and Hedges, 1994). We conducted a MEDLARS search of the literature published between January 1966 and March 2005, as well as a review of Cancer Lit and the CD-ROM version of Current Contents. The search criteria included all languages. The search terms used were talc exposure and ovarian neoplasms. If a series of articles was published, all data were retrieved from the most recent article. The literature search also included hand searches of bibliographies of published reports, review articles and textbooks.

The initial citations (in the form of abstracts) from this literature search were screened by a physician investigator to exclude those that did not meet inclusion criteria. Reasons for rejection included study designs other than case–control, cohort or randomized controlled trials; animal or in-vivo studies; abstracts; review articles and non-peer reviewed articles. Eligibility criteria included, observational studies or clinical trials enrolling patients with histologically proven ovarian tumors of all histologies, studies enrolling only adult patients (i.e. 18 years or older), availability of data documenting type of talc exposure, in this instance, dusting of diaphragms, and availability of odds ratios or relative risks with 95% confidence intervals for each report or availability of raw data to calculate these parameters.

Statistical analysis

We performed data analysis according to meta-analytic procedures described by Greenland (1986). This method of meta-analysis is a general variance-based method employing confidence intervals. As the variance estimates are based on the adjusted measures of effect, the confidence interval methods do not ignore confounding and are the preferred methodology for pooling observational studies.

For each included study, we derived odds ratios reflecting the risk of developing ovarian cancer associated with the practice of dusting contraceptive diaphragms with cosmetic talc and determined the natural logarithm of the estimated relative risk for each data set followed by calculation of an estimate of the variance. We used the estimate of the 95% confidence interval from each study to calculate the variance of each study's measure of effect.

We calculated a weight for each included analysis as 1/variance followed by a summation of the weights. We then determined the product of the study weight and the natural logarithm of the estimated relative risk and performed a summation of these products. Finally, a summary relative risk and 95% confidence interval were determined.

Before the estimation of a summary relative risk, a statistical test for homogeneity was performed (Q). This procedure tests the hypothesis that the effect sizes are equal in all of the included studies (Greenland, 1986). If Q exceeds the upper tail critical value of χ^2 ($P < 0.10$) at $k-1$ d.f. (where k equals the number of studies analyzed or the number of comparisons made), the observed variance in study effect sizes is significantly greater than what would be expected by chance if all studies shared a common population effect size. If the hypothesis that the studies are homogenous is rejected, the studies do not measure an effect of the same size. In this instance, calculation of a pooled estimate of effect (i.e. relative risks) may be of questionable validity. Possible explanations for the observed heterogeneity must be sought to provide the most rational interpretation of the summary relative risk. Sensitivity analyses and or further stratified analyses are then performed based on the magnitude of Q.

Results

The literature search yielded 17 studies that appeared to meet protocol specifications and full papers were obtained for review (Hartge *et al.*, 1983; Richardson *et al.*, 1985; Whittemore *et al.*, 1988; Booth *et al.*, 1989; Harlow and Weiss, 1989; Chen *et al.*, 1992; Harlow *et al.*, 1992; Rosenblatt *et al.*, 1992; Tzonou *et al.*, 1993; Purdie *et al.*, 1995; Cook *et al.*, 1997; Goddard *et al.*, 1998; Cramer *et al.*, 1999; Gertig *et al.*, 2000; Ness *et al.*, 2000). Upon further review, nine of these met the specified inclusion criteria. Table 1 provides an overview of the nine reports included in the meta-analysis (Hartge *et al.*, 1983; Richardson *et al.*, 1985; Whittemore *et al.*, 1988; Booth *et al.*, 1989; Harlow and Weiss, 1989; Harlow *et al.*, 1992; Rosenblatt *et al.*, 1992; Cook *et al.*, 1997; Ness *et al.*, 2000). A total of 2281 ovarian cancer cases and 3608 controls were enrolled in nine case–control studies. Table 1 also specifies which reports were hospital based versus those that were population based. Only Cook *et al.* (1997) and Harlow and Weiss (1989) used both population-derived cases and controls. All of the other studies listed as 'population based' used hospital-derived cases. The individual study odds ratios listed in Table 1 reflect the odds of exposure in cases versus controls, with an odds ratio greater than one suggesting a positive association, that is, an increased risk of ovarian cancer among women using talc-dusted diaphragms.

Before combining all studies to derive a summary estimate of effect (i.e. a summary relative risk) a statistical test for heterogeneity was performed (Q). This gave a value of Q equal to 10.75. With eight degrees of freedom, the P value associated with a Q of this size is 0.22. This indicates that the studies are homogeneous; that is, the studies are measuring an effect of similar

Table 1 Overview of included studies

Study (year)	Number of cases/controls	Percentage eligible cases included	Adjusted OR	95% CI	Adjustments to OR	Epithelial tumors only	Borderline tumors incl.	Stratification by histology	H/P
Booth *et al.* (1989)	235/451	84	0.75	0.85 2.02	Age, SES	Y	Y	N	H
Cook *et al.* (1997)	313/422	64	0.80	0.40 1.40	Age	Y	N+	Y	P
Cramer *et al.* (1982)	215/215	72	1.56	0.62 3.88	Parity, menstrual status	Y	Y	Y	P
Harlow *et al.* (1992)	235/239	59	1.20	0.60 2.40	Parity, education, marital status, religion, use of sanitary napkins, douching, age, weight	Y	Y	Y	P
Harlow and Weiss, 1989	116/158	68	0.50	0.20 1.30	Age, parity, use of oral contraceptives	N/A	All	N/A	P
Hartge *et al.* (1983)	135/171	69	0.80	0.40 1.40	Age, race, hospital	Y	Unknown	N	H
Ness *et al.* (2000)	767/1367	61	0.60	0.30 1.20	Age, gravity, race family HX ovarian cancer, oral contraceptive use, tubal ligation, hysterectomy, breast feeding	Y	Y	N	P
Rosenblatt *et al.* (1992)	77/46	55	3.0	0.80 10.8	Obesity, SES, religion, number of live births, OC use	Y	Unknown	N	H
Whittemore *et al.* (1988)	188/539	NG	1.5	0.63 3.58	Parity, use of oral contra ceptives	Y	Unknown	N	H

SES, socio economic status; OR, odds ratio; CI, confidence interval; H/P, hospital based/population based; N+, separate analyses done for borderline versus invasive tumors.

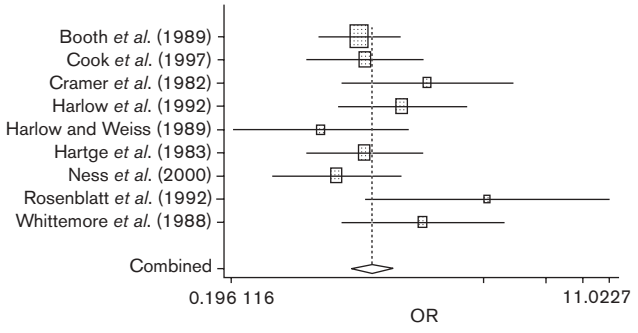
magnitudes. Given the lack of statistical heterogeneity, the data were pooled for calculation of a summary relative risk.

Table 1 shows that adjusted odds ratios ranged from 0.60 (Booth *et al.*, 1989) to 3.0 (Rosenblatt *et al.*, 1992), with adjustment parameters specified along with 95% confidence intervals. Of note, none of the reports showed a statistically significant odds ratio. Initial pooling of data from all nine reports yielded a summary relative risk of 1.03 with a 95% confidence interval of 0.80–1.33, a non-statistically significant result suggesting no association between talc/diaphragm use and ovarian cancer risk (see Fig. 1).

Upon closer scrutiny of the available data, further sensitivity analyses were performed as described below. The data provided by Booth *et al.* (1989) did not explicitly provide data on talc use via contraceptive diaphragms and such use could only be assumed. As the data were questionable in this respect they were dropped from the analysis and a summary relative risk was recalculated. The resultant relative risks was 1.12 with a 95% confidence interval of 0.84–1.48. Therefore, the results remained statistically non-significant despite removal of these data from the summary estimate of effect.

The report by Harlow *et al.* (1992) also represents a potential problem for statistical pooling as the cases in this instance were all patients with 'borderline ovarian tumors'. The exact nature of borderline ovarian tumors in terms of a relationship with their invasive counterparts remains unclear, with some data suggesting differences in epidemiology and etiology (Riman *et al.*, 2001). Whether borderline tumors are precursors of invasive cancers or a separate disease entity is a matter of debate. We therefore recalculated a summary relative risk without inclusion of data from the study by Ness *et al.* (2000). This gave a relative risk of 1.09 with a 95% confidence interval of (0.84–1.41), a non-statistically significant result.

Fig. 1



Forest plot of summary relative risk derived by pooling all available studies using adjusted odds ratios (OR).

All studies except that of Hartge *et al.* (1983) are full research reports with the study by Ness *et al.* (2000) published as a 'Letter to the editor'. Publication in this format is potentially problematic owing to issues related to the 'quality' of the presented data. Letters to the editor normally do not undergo the same type of editorial scrutiny as full research papers. In addition, by their nature, letters are brief notes with limited details presented, precluding rigorous evaluation of methods, results and associated conclusions. In order to address these issues, we dropped the study by Hartge *et al.* from the pooled analysis and, again, recalculated a summary relative risk. This gave a relative risk of 1.07 with a 95% confidence interval of 0.82–1.40. Again, this represents a non-significant finding.

In a prior meta-analysis (Huncharek *et al.*, 2003), we demonstrated a possible bias among studies examining the perineal talc use/ovarian cancer association based on the source of cases. That is, our study suggested that population-based studies may spuriously show a causal association secondary to exposure misclassification to a 'treatment effect' among population-derived cases. Some patients with ovarian cancer will undergo treatment with radiation, chemotherapy and/or surgery. Side effects from treatment may prompt talc use among some of these individuals. Patients may not always make the distinction between pre-diagnosis and post-treatment use. Exposure misclassification among 'prevalent' cases may cause a spurious finding of an association when none, in fact, exists. We therefore recalculated the summary relative risk excluding the studies by Cook *et al.* (1997) and Harlow and Weiss (1989) as these were the only two reports that utilized population-derived cases and controls. The resultant relative risk was 1.15 with a non-statistically significant odds ratio of 0.87–1.53.

Furthermore, this suggests no association between talc use and increased ovarian cancer risk. In fact, if data from the studies by Cook *et al.* (1997) and Harlow and Weiss (1989) are statistically pooled, the summary relative risk is 0.67 with a non-significant confidence interval (i.e. 0.34–1.35). The fact that the population-based relative risk is in the opposite direction (i.e. favoring a protective effect for talc) to that shown in the other case–control studies, further supports the existence of bias in these analyses.

Another methodological consideration is the fact that the definitions of the control groups used across all nine studies are not completely comparable. Some reports defined controls as 'never having used talc' (e.g. Ness *et al.*, 2000), while others used controls defined as not

having used talc on diaphragms (e.g. Cook *et al.*, 1997). We therefore calculated crude odds ratios and 95% confidence intervals using data supplied in the available studies and recalculated a summary relative risk to ensure that the analysis using adjusted odds ratio was not spurious (Table 2). The resultant relative risk was 0.86 (0.59–1.40) (see Fig. 2), a non-statistically significant result suggesting no association between talc use on diaphragms and increased ovarian cancer risk (see Fig. 2). Of note, the test for heterogeneity for this latter analysis gave a value for Q of 7.20 with a P value of 0.52.

Discussion

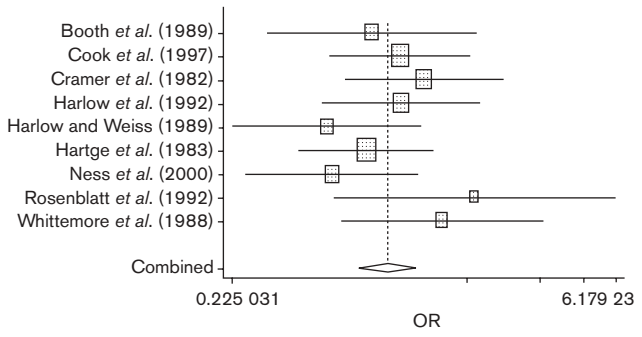
Talc is an important industrial mineral for a number of reasons including its resistance to heat, electricity and acids and its relatively low price. It is used in many commercial applications because of its lamellar platy nature, softness, whiteness, chemical inertness, high melting point and hydrophobic features, among others. For instance, talc is used in the plastic industry owing to its inertness, superior electrical and thermal resistance and its ability to improve the quality of plastic surfaces. It also finds application in the paint industry to increase the smoothness of paint products and in paper manufacturing to reduce the usage of expensive whitening agents because of its high brightness.

Table 2 Crude odds ratios and 95% confidence intervals for included studies

Study (year)	Crude OR	95% CI	Variance	Weight
Booth *et al.* (1989)	0.75	0.33 2.02	0.175	5.70
Cook *et al.* (1997)	0.96	0.52 1.76	0.097	10.2
Cramer *et al.* (1982)	1.18	0.59 2.35	0.125	7.99
Harlow *et al.* (1992)	0.97	0.49 1.92	0.121	8.24
Harlow and Weiss, 1989	0.51	0.22 1.13	0.184	5.43
Hartge *et al.* (1983)	0.72	0.40 1.30	0.090	11.1
Ness *et al.* (2000)	0.53	0.25 1.13	0.147	6.80
Rosenblatt *et al.* (1992)	1.82	0.55 6.34	0.373	2.68
Whittemore *et al.* (1988)	1.38	0.57 3.28	0.204	4.91

OR, odds ratio; CI, confidence interval.

Fig. 2



Forest plot of summary relative risk derived by pooling all available studies using crude odds ratios (OR).

Mineral talc is a magnesium silicate hydroxide belonging to the mineral class, silicate and subclass phyllosilicate. It belongs to the clay mineral group, an important subgroup within the phyllosilicates that contain large percentages of water trapped between the silicate sheets. Clay minerals are divided into four major groups: the kaolinite group, the montmorillonite/smectite group, the illite group and the chlorite group. Talc is a member of the montmorillon/smectite group along with pyrophyllite, vermiculite, sauconite, saponite and nontronite.

Talc also forms pseudomorphs, that is false shapes, of other minerals, replacing them on an atom by atom basis. For instance, talc forms pseudomorphs of quartz, pyroxene, olivine and amphiboles. In nature, it can also be found in association with a number of other minerals, such as serpentine, quartz, olivine and biotite.

In 1982, Cramer *et al.* (1982) published a case–control study suggesting an association between cosmetic talc use on the perineum and increased ovarian cancer risk. Women dusting the perineum with talc or dusting sanitary napkins showed a near doubling of ovarian cancer risk. Unfortunately, in addition to a number of methodological limitations plaguing this report (e.g. only 45% of eligible controls participating), it is important to point out the flawed premise on which it is based. Cramer *et al.* (1982) cite the 'chemical relationship between talc and asbestos' as a major reason for assuming that talc may also be a human carcinogen and that '…the mineral talc is a specific hydrous magnesium silicate chemically related to several asbestos group minerals and occurring in nature with them'.

The above-cited justification for the Cramer *et al.* (1982) study and subsequent work examining a possible cosmetic talc/ovarian cancer link is misguided for a number of reasons. Despite the fact that talc and various forms of asbestos are silicates, they are structurally distinct and belong to different mineral groups and subgroups. That is, amphibole minerals (e.g. tremolite) are inosilicates while talc is a member of the silicate subclass phyllosilicate and the group, clay or montmorillonite/smectite. While serpentines, including serpentine asbestos, are also phyllosilicates, serpentine minerals belong to the kalolinite–serpentine group. The asbestos varieties of serpentine are structurally different from other members of the serpentines in that their brucite layers and silicate layers bend into tubes that produce fibers. Non-fibrous serpentine does not have carcinogenic properties and it is clear that the physical structure of serpentine asbestos is responsible for its disease-causing

potential, not its atomic constituents. It simply does not follow, therefore, that one should assume that talc is carcinogenic simply because it is a silicate and a member of the phyllosilicate subgroup. Structure dictates toxicity/carcinogenicity, not chemical composition.

It is true that in nature, mineral talc can be found in association with both serpentine and amphibole minerals, including the asbestos varieties. It is crucial to understand that the carcinogenic potential of asbestos is well known and abundantly documented in the medical and epidemiological literature (Huncharek, 1986; Mossman and Gee, 1989). Cramer *et al.*'s argument suggesting that pure talc is carcinogenic is based solely on 'guilt by association' rather than on scientific fact. If one is exposed to a mixture of talc and asbestos, it is reasonable to expect a carcinogenic effect as it contains a known carcinogen. To then suggest that talc is also carcinogenic simply owing to the fact that it is sometimes found in association with various asbestos minerals in nature is not logical. This reasoning ignores a large body of data regarding the mineralogy of silicates and fails to acknowledge the lack of supporting biological or in-vitro data documenting any carcinogenic potential of pure talc (i.e. uncontaminated by asbestos). A commercial product containing asbestos-contaminated talc could certainly pose a health risk and although prior to the mid-1970s some consumer talc products did, in fact, contain such contamination, the carcinogenic entity is asbestos, not talc (Rohl *et al.*, 1976). It is important to note that since that time, talc product manufacturers voluntarily ensured that such products are asbestos free. Despite this fact, even some recent studies looking at the perineal talc dusting/ovarian cancer risk connection show a weak association (e.g. Mills *et al.*, 2004), further suggesting a spurious finding.

Other evidence that indicates that talc and asbestos have dissimilar biological properties is the fact that talc has been used for decades as a sclerosing agent for both benign and malignant pleural effusions (Viskum *et al.*, 1989). Long-term follow-up studies of these patients have not shown even a single case of lung cancer or mesothelioma resulting from introduction of talc to the pleural cavity (Viskum *et al.*, 1989; Shaw and Agarwal, 2004). Epidemiological studies of talc miners and millers also fail to demonstrate an increased cancer risk (Rubino *et al.*, 1976; Gamble, 1993). In-vivo implantation and injection using asbestos of various types, in contrast, unequivocally induce tumors in experimental animals (Huncharek, 1986).

Despite the above-noted problems, the idea that cosmetic talc poses a possible ovarian cancer risk persists. As reviewed in the present paper and elsewhere (Richardson *et al.*, 1985; Tortolero-Luna and Mitchell, 1995) numerous investigators have examined this possible relationship in a variety of case–control studies and at least one cohort study (e.g. Gertig *et al.*, 2000). Most of these categorized talc use as 'ever versus never' used while others further stratified by particular types of use, for example, perineal dusting, sanitary napkin dusting, condoms, etc. Results differ across studies, with some showing no association (Rosenblatt *et al.*, 1992) while others suggests a 'weak effect' (Purdie *et al.*, 1995), that is odds ratios below 1.5.

In addition to the obvious problems with the premise put forth by Cramer *et al.* (1982) and others, validity of the weak effect shown in a number of other epidemiological studies also remains questionable. The major weaknesses of the existing database include (Boger-Meigiddo and Weiss, 2005) the relatively small sample size of most reports, which limits the statistical power to detect an effect (Richardson *et al.*, 1985), the lack of consistent positive association across studies (Baker and Piver, 1994), the absence of a demonstrable dose–response relationship (Daly and Obrams, 1998), the lack of supporting evidence of talc carcinogenicity from animal or in-vitro analyses (Tortolero-Luna and Mitchell, 1995) and the possible presence of uncontrolled confounding producing a spurious positive association. In fact, some of the available observational studies show an inverse dose–response (Ness *et al.*, 2000) that weighs against a causal association. In addition, no plausible biological mechanism capable of explaining how talc could induce ovarian malignancies exists.

In a study, Heller *et al.* (1996) examined talc particle counts in ovarian specimens from 24 women undergoing incidental oophorectomy and compared these counts with reported frequency and duration of talc use. The study sought to examine the hypothesis of a dose-related risk of epithelial ovarian cancer with perineal talc exposure. Women were considered 'exposed' if they reported talc application to undergarments or directly to the perineum. Talc was detected in all ovaries by either polarized light or electron microscopy. No relationship was found between cosmetic talc burden in healthy ovarian tissue and lifelong perineal talc dusting determined by either microscopic methods. This study raises further questions regarding whether reported associations between perineal talc exposure and ovarian tumors in observational studies reflects a carcinogenic action of talc. The validity of these epidemiologic associations has also been questioned because it is unknown whether talc dust in the perineal area can actually penetrate the female reproductive tract and then translocate to the ovaries against physiological forces working in the opposite direction. The work of Heller *et al.* clearly brings this into question.

Although the epidemiological literature focuses primarily on external perineal exposure to talc, a more valid

assessment of the 'talc hypothesis' would appear to be provided by examining the ovarian cancer risk associated with talc dusting of diaphragms. This particular use of talc results in direct female reproductive tract exposure. Although data on the use of talc-dusted diaphragms have been reported in some epidemiological studies, this literature fails to garner the attention devoted to perineal dusting and no systematic evaluation of this particular literature is available. This probably reflects the fact that perineal dusting is a more common practice than dusting contraceptive diaphragms. Nonetheless, exposure via this latter route is, intuitively, a better 'model' for testing whether talc represents a risk factor for ovarian cancer as the exposure is directly to the female genital tract. Consequently, we performed the above-detailed meta-analysis pooling all available published data on this topic.

Using accepted meta-analytic techniques our analysis was unable to demonstrate any increased risk of ovarian cancer associated with use of talc-dusted diaphragms. Despite performing a number of sensitivity analyses to test the robustness of our findings, the pooled data from over 5000 cases and controls failed to show a positive association. In some studies, the odds ratio was calculated based on an inappropriate control group; for example, individuals who reported no exposure to any talc. For these studies, the crude odds ratio was recalculated based on women who never used talc-dusted diaphragms as the reference group. This summary relative risk was also statistically non-significant.

In summary, our present report, along with our prior meta-analysis pooling data from studies examining the possible ovarian cancer risk associated with perineal talc dusting (Huncharek *et al.*, 2003), does not provide evidence of a causal relationship. In the context of 'weak associations', many sources of bias and uncontrolled confounding can contribute to the finding of a spurious association. Recall bias in case–control studies, lack of a demonstrated dose–response in many published analyses, lack of a coherent biological mechanism for possible talc carcinogenicity and lack of supporting animal or in-vitro data demonstrating the carcinogenic potential of talc all argue against a causal relationship. These limitations and inconsistencies have also been discussed in detail elsewhere (Wehner, 1994; Muscat and Barish, 1998). As ovarian cancer remains a major cause of cancer-related morbidity and mortality in the United States, further work is needed to clearly define modifiable risk factors in an attempt to improve disease prevention.

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